15. (Amended) A humanized antibody that is specifically reactive with human CTLA4, wherein the antibody comprises the amino acid sequence shown in SEQ ID NO: 10.

REMARKS

Applicants have reviewed the specification and corrected minor typographical errors.

The disclosure stands objected to because blanks are present in the specification on pages 4, 5, and 28 for ATCC and hybridoma designations of the CTLA4 antibodies. Applicants respectfully request that the objection be held in abeyance until such time as there is allowable subject matter.

STATUS OF THE CLAIMS

Claims 1-23 are pending. Claims 16-23 have been withdrawn from further consideration by the Examiner as being drawn to a non-elected invention. Claims 1-15 are currently under consideration. Applicants gratefully acknowledge that the Examiner has withdrawn the species election requirement regarding the toxic moiety.

Claim 1 has been amended herein to more particularly point out the subject matter of the invention. Support for the amendment is found in the specification on pages 1, line 9-page 3, line 5; page 7, lines 23-32; pages 67, line 28-page 68, line 2 and page 69, lines 13-25.

Claim 7 has been amended to more particularly point out the invention. Support for this amendment is found on page 78, line 19-page 79, line 13; page 5, lines 22-25; and Figure 2B. Figure 2B presents ELISA results indicating the E46 CTLA4 mutant

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(position 83 in SEQ ID NO:2) binding to antibody 26 is reduced by about 80% compared to the WT CTLA4.

Claim 12 has been cancelled herein.

Claims 14 and 15 have been amended to merely correct a typographical error identified by the Examiner. Applicants thank the Examiner for pointing out this inadvertent error.

No new matter has been added by any amendment. The scope of the claims has not been narrowed by any amendment.

Written Description Rejection Under 35 U.S.C. § 112

Claim 1 stands rejected as allegedly failing to comply with the written description requirement of 35 U.S.C. § 112 first paragraph. Claim 1 recited "a molecule expressed only on an activated T cell." The Examiner alleges that the specification as filed does not reasonably convey to the skilled artisan that Applicants were in possession of the invention at the time the application was filed because, according to the Examiner, the specification only discloses CTLA4 as an example of a molecule expressed only on an activated T cell. CTLA4 is not the only example of a molecule expressed on the surface of an activated T cell. The specification also discloses ICOS (page 2, lines 19-20).

Applicants believe the rejection is in error and submit the specification describes the invention in sufficient detail to demonstrate possession of the claimed subject matter. (See e.g. page 3, lines 6-10; page 8, lines 25-31). Nonetheless, in order to expedite prosecution Applicants have amended claim 1, thus obviating the rejection. Support for the amendment is found in the specification on pages 1, line 9-page 3, line

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5; page 7, lines 23-32; pages 67, line 28-page 68, line 2 and page 69, lines 13-25. Applicants request that the Examiner withdraw this written description rejection.

Enablement Rejection Under 35 U.S.C. § 112

Claim 1 stands rejected under 35 U.S.C. § 112 first paragraph. The Examiner admits the claim is enabled for an antibody-toxic moiety conjugate comprising an antibody that specifically recognized CTLA4 and certain other art recognized molecules, but alleges the claimed invention is not enabled for any molecule expressed only on a T cell. According to the Examiner, the specification does not provide sufficient guidance regarding how to identify other molecules expressed only on activated T cells. The Examiner further alleges only two examples of T cell activation markers (CTLA4 and ACT4) are disclosed in the specification or the art.

This allegation is inaccurate. Applicants also disclose ICOS (page 2, lines 19-20). Applicants believe the specification coupled with knowledge in the art is sufficient to enable the invention as claimed. Moreover, methods of identifying other activation markers were known in the art (see e.g. U.S. Patent No. 5,821,332, column 25, line 1-column 3, line 10). Nonetheless, to expedite prosecution Applicants have amended claim 1 herein, thus obviating the rejection. Amended claim 1 is enabled (*see e.g.* page 1, line 9-page 3, line 4).

Claims 14 and 15 stand rejected under 35 U.S.C. § 112 as allegedly not enabled by the specification. The Examiner objects to use the indefinite article "an" and has suggested amending the claim to recite the definite article "the". The Examiner alleges use of "an" reads on subsequences of the variable domain found outside the CDRs and

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concludes that the specification does not enable the skilled artisan to make a humanized antibody from these subsequences.

Applicants believe the Examiners conclusion is in error because the specification does enable an antibody comprising subsequences of the variable domain (See e.g. page 26, lines 5-15; page 31, line 1-page 34, line 13). Furthermore, the Examiner's reliance on Bendig to support the proposition that the art teaches all six CDRs are necessary for humanizing an antibody is misplaced. U.S. Patent No. 6,207,156 (Kuchroo) (already of record) contradicts this notion (see column 5, lines 9-16). Nonetheless, in order to expedite prosecution, Applicants have amended claims 14 and 15 herein pursuant to the Examiner's suggestions. The rejection is thus, obviated by this amendment.

Lastly, the Examiner has rejected claim 12 as requiring deposit of any antibodies that may be recited in this claim. Claim 12 has been cancelled herein, thus the rejection is obviated. Applicants reserve the right to pursue the subject matter recited in claim 12 at a later date.

Indefiniteness Under 35 U.S.C. § 112

Claim 7 stands rejected as being indefinite under 35 U.S.C. § 112. The Examiner alleges that the term "modulate" renders the claim indefinite. Applicants submit the term is not indefinite and that a skilled artisan would recognize its meaning in light of the disclosure in the specification. The specification teaches the substitution of amino acid 83 in the amino acid sequence of human CTLA4 shown in SEQ ID NO: 2 either decreases binding or has little or no effect on binding. (See page 78, line 19-

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page 79, line 13 and Figure 2). Nonetheless, in order to expedite prosecution, Applicants have amended claim 7 to recite "reduced binding of the antibody by at least about 80%." Figure 2B presents ELISA results indicating the E46 CTLA4 mutant (position 83 in SEQ ID NO:2) binding is reduced by at least about 80% compared to the WT CTLA4. The rejection is thus obviated by the amendment.

Claim 12 is rejected by the Examiner as being indefinite under 35 U.S.C. § 112. The Examiner rejected the claim because the claim does not recite the ATCC accession numbers for the hybridomas producing the claimed antibody-toxic conjugates. Claim 12 has been cancelled herein. The rejection is thus obviated by this amendment.

Anticipation Rejection Under 35 U.S.C. § 102(b)

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,821,332 (Godfrey). Claim 1 recites "an antibody-toxic moiety conjugate comprising an antibody that specifically recognizes a molecule expressed only on activated T cells . . . ." The Examiner alleges that Godfrey teaches the human polypeptide ACT4 which is only expressed on activated T cells. According to the Examiner, Godfrey also teaches antibody-toxic moiety conjugates specific to ACT4. The Examiner concludes the claimed invention is, thus, anticipated. The conclusion is erroneous.

Consideration of the whole Godfrey reference yields a different conclusion. Godfrey does not teach ACT4 is expressed only on activated T cells. Godfrey teaches ACT4 is present on a B-lymphoid cell line and PMA activated monocytes as well as a transformed T cell line (*see e.g.* column 25, lines 20-45). "A claim is anticipated only if

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each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The Godfrey reference does not meet this standard and therefore does not anticipate claim 1. Nonetheless, in order to expedite prosecution Applicants have amended claim 1, to recite B7 costimulatory molecule and costimulatory receptor. ACT4 is not a B7 costimulatory molecule or a costimulatory receptor. This amendment obviates the rejection. Thus, Applicants request that the Examiner withdraw this rejection.

The Rejection Under 35 U.S.C. § 103(a)

Claims 1-7, 10-11 and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Godfrey and U.S. Patent No. 6,207,156 (Kuchroo). The Examiner alleges Kuchroo teaches monoclonal antibodies to CTLA4, but admits that Kuchroo does not teach antibody toxic-moiety conjugates. The Examiner alleges Godfrey teaches antibody-toxic moiety conjugates specific to ACT4, a polypeptide allegedly expressed only on activated T cells. The Examiner concludes the claimed invention is obvious in light of Godfrey combined with Kuchroo. The conclusion is erroneous.

The Claimed Invention Is Not Prima Facie Obvious

MPEP § 2143 provides the standard required to establish a prima facie case of obviousness. "First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine what the reference teaches. Second,

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there must be a reasonable expectation of success. Finally, the prior art reference (or references combined) must teach or suggest all the claim limitations."

The motivation to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not the applicant's disclosure *In re Vaeck,* 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). The references must be considered as a whole and must suggest the desireability, and thus the obviousness of making the combination. *Hodosh v. Block Drug Col, Inc.,* 786 F.2d 1136, 1143 n.5, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); MPEP § 2141. The Patent and Trademark Office (PTO) bears the burden of initially establishing a prima facie case of obviousness. MPEP § 2142. The PTO has not met its burden in the instant case.

No Motivation Exists To Combine The Cited References

A skilled artisan would not be motivated to combine Kuchroo with Godfrey because each reference teaches opposing results from the administration of the antibody. Godfrey teaches that antibody toxic moiety conjugates can be used to kill cells expressing ACT4. (*see* column 22, lines 24-28 "anti-ACT-4 receptor antibodies with effector functions or which are conjugated to toxins . . . are capable of selectively killing activated T cells").

In contrast, Kuchroo teaches that peptides binding to CTLA4 act as immune response enhancers (i.e. stimulate T cell activation/proliferation) (See e.g. column 2, line 20-column 4, line 50, stating "these peptides have particular utility as pharmaceuticals for the immune therapy of T-cell proliferation sensitive disorders because of their ability to co-stimulate T-cell proliferation . . . . The peptides of the

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invention when administered in conjunction with a chemotherapeutic agent enhance the tumoricidal effect of the chemotherapeutic agent by stimulated T cell proliferation . . . . The peptide may be an intact soluble monoclonal antibody." (emphasis added). Kuchroo does not teach antibody-toxic moiety conjugates. Nothing in Kuchroo suggests CTLA4 specific antibodies can be used to suppress an immune response or kill CTLA4 positive cells.

The instant claims, however, recite an "antibody toxic moiety conjugate." The Examiner has pointed to nothing in either reference to explain why a skilled artisan would want to target CTLA4 with a antibody toxic moiety conjugate when Kuchroo teaches that antibodies to CTLA4 are immunostimulatory and cause T cell proliferation. In contrast, an antibody-toxic moiety conjugate as taught by Godfrey eliminates the target cell, but does not cause it to proliferate as Kuchroo suggests CTLA4 antibodies do.

The Examiner alleges that a motivation to combine exists because Godfrey teaches the desirability of using multiple targets to achieve immune suppression. But, the Examiner has not explained why a skilled artisan would include an immune enhancer (as taught by Kuchroo) as a target for an antibody-toxin conjugate.

The Examiner is reminded the motivation to combine must be found in the prior art and not based on hindsight in light of the Applicant's disclosure. *Vaeck*, *supra*. Applicants respectfully submit the Examiner has not established the requisite motivation based on the cited art.

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No Reasonable Expectation of Success Exists In Combining The Cited References

In addition, there would be no reasonable expectation of success in combining Kuchroo with Godfrey because they describe molecules that utilize distinct signaling pathways. CTLA4 is part of the B-7 costimulatory pathway. In contrast, ACT4 is a member of the nerve growth factor receptor family (Godfrey column 9, lines 40-46). Godfrey states: "These data indicate that ACT-4 receptors should be classified as early activation antigens. . ." (column 10, lines 8-10). In the very next sentence Godfrey stresses that ACT4 is unique among activation antigens. A skilled artisan therefore would not be able to generalize Godfrey's teachings to other molecules. Given that ACT4 and CTLA4 signal through distinct pathways and given that Godfrey teaches ACT4 is unique among activation antigens a skilled artisan would have no reasonable expectation of success in combining the teachings of the two references.

Because neither the requisite motivation to combine or a reasonable expectation of success can be found in the cited references, the claimed invention is not prima facie obvious and Applicants respectfully request withdrawal of the rejection.

Hamann Combined With Godfrey And Kuchroo Does Not Render Claims 8 And 9 Prima Facie Obvious

Additionally, claims 8-9 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Godfrey, combined with Kuchroo in view of U.S. Patent No. 5,773,001 (Hamann). Claim 8 recites the toxic moiety is a carbohydrate. Claim 9 recites the carbohydrate is calicheamicin. Hamann teaches antibodies conjugated with calicheamicin. Hamman does not teach targeting molecules expressed on activated T

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cells. The Examiner thus relies on Hamann as allegedly teaching antibodies conjugated to carbohydrates generally, and calicheamicin specifically. Hamann, however, does not compensate for the deficiencies in the Godfrey and Kuchroo. A skilled artisan reading Hamann would still have no motivation to combine Godfrey with Kuchroo, as Hamann only provides information on conjugating antibodies with calicheamicin--it does not address targeting molecules expressed on activated T cells. Similarly, no reasonable expectation of success can be found in combining the cited references for the same reasons discussed above regarding Godfrey and Kuchroo. Thus, claims 8 and 9 are not prima facie obvious. Applicants respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: February 24, 2003

By: E Stewart Mittler
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APPENDIX OF AMENDMENTS
VERSION WITH MARKINGS TO SHOW CHANGES

Please amend the specification as follows:

Please replace the paragraph beginning on page 4, line 11 with the following paragraph::

> In another aspect, the invention pertains to a humanized antibody that is specifically reactive with human [CLTA4] CTLA4, wherein the antibody comprises an amino acid sequence shown in SEQ ID NO: 8.

Please replace the paragraph beginning on page 4, line 14 with the following paragraph:

> In yet another aspect, the invention pertains to a humanized antibody that is specifically reactive with human [CLTA4] CTLA4, wherein the antibody comprises an amino acid sequence shown in SEQ ID NO: 10.

Please replace the paragraph beginning on page 7, line 23 with the following paragraph:

> As used herein, the term "costimulatory receptor" includes receptors which transmit a costimulatory signal to a immune cell, *e.g.*, CD28. As used herein, the term "inhibitory receptors" includes receptors which transmit a negative signal to an immune cell (*e.g.*, CTLA4). An inhibitory signal as transduced by an inhibitory receptor can occur even if a costimulatory receptor (such as CD28) [in]is not present on the immune cell and, thus, is not simply a function of

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competition between inhibitory receptors and costimulatory receptors for binding of costimulatory molecules (Fallarino *et al.* (1998) *J. Exp. Med.* 188:205). Transmission of an inhibitory signal to an immune cell can result in unresponsiveness or anergy or programmed cell death in the immune cell.

Please replace the paragraph beginning on page 68, line 3 with the following paragraph:

Antibodies that mimic interaction of CTLA4 with a costimulatory molecule (*e.g.*, CTLA4 activating antibodies or multivalently presented antibodies) can be identified by their ability to inhibit immune cell proliferation and/or effector function or to induce anergy when needed to an *in vitro* assay. For example, cells can be cultured in the presence of an agent that stimulates signal transduction via an activating receptor. A number of art recognized readouts of cell activation can be employed to measure the ability of an antibody to transmit a negative signal, *e.g.*, by measuring its effect on cell proliferation or T cell effector function (*e.g.*, cytokine production) in the presence of the activating agent. The ability of a test agent to block its activation can be readily determined by measuring the ability of the agent to effect a decrease in proliferation or effector function being measured.

Please amend the claims as follows:

1. An antibody-toxic moiety conjugate comprising an antibody that specifically recognizes [a molecule expressed] (a) at least one of a B7 costimulatory molecule and a costimulatory receptor expressed [only] on activated T cells and (b) a toxic moiety.

7. An antibody-toxic moiety conjugate of claim 2, wherein the substitution of amino acid 83 in the amino acid sequence of human CTLA4 shown in SEQ ID NO: 2 results in [modulation of] reduced binding of the antibody by at least about 80% compared to an antibody without the substitution of amino acid 83.

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14. A humanized antibody that is specifically reactive with human [CLTA4] CTLA4, wherein the antibody comprises the [an] amino acid sequence shown in SEQ ID NO: 8.

15. A humanized antibody that is specifically reactive with human [CLTA4] CTLA4, wherein the antibody comprises the [an] amino acid sequence shown in SEQ ID NO: 10.

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